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Network architecture underlying basal autonomic outflow: Evidence from frontotemporal dementia

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AUTONOMIC NETWORK ARCHITECTURE

Running Title: AUTONOMIC NETWORK ARCHITECTURE

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Abstract

The salience network is a distributed neural system that maintains homeostasis by regulating autonomic nervous system activity and social-emotional function. Here we examined how within-network connectivity relates to individual differences in human (including males and females) baseline parasympathetic and sympathetic nervous activity. We measured resting autonomic nervous system physiology in 24 healthy controls and 23 patients with behavioral variant frontotemporal dementia (bvFTD), a neurodegenerative disease characterized by baseline autonomic deficits. Participants also underwent structural and task-free functional magnetic resonance imaging. First, we used voxel-based morphometry to determine whether salience network atrophy was associated with lower baseline respiratory sinus arrhythmia (RSA; a parasympathetic measure) and skin conductance level (SCL; a sympathetic measure) in bvFTD. Next, we examined whether functional connectivity deficits in 21 autonomic-relevant, salience network node-pairs related to baseline autonomic dysfunction. Lower baseline RSA was associated with smaller volume in left ventral anterior insula (vAI), weaker connectivity between bilateral vAI and bilateral anterior cingulate cortex (ACC), and stronger connectivity between bilateral ACC and bilateral hypothalamus/amygdala. Lower baseline SCL, in contrast, was associated with smaller volume in inferior temporal gyrus, dorsal mid-insula, and hypothalamus; weaker connectivity between bilateral ACC and right hypothalamus/amygdala; and stronger connectivity between bilateral dorsal anterior insula and periaqueductal gray. Our results suggest that baseline parasympathetic and sympathetic tone depend on the integrity of lateralized salience network hubs (left vAI for parasympathetic and right hypothalamus/amygdala for sympathetic) and highly calibrated ipsilateral and contralateral network connections. In bvFTD, deficits in this system may underlie resting parasympathetic and sympathetic disruption.

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89 Significance Statement

90 The salience network maintains homeostasis and regulates autonomic nervous system activity.
91 Whether within-network connectivity patterns underlie individual differences in resting
92 parasympathetic and sympathetic nervous system activity, however, is not well understood. We
93 measured baseline autonomic nervous system activity in healthy controls and patients with
94 behavioral variant frontotemporal dementia, a neurodegenerative disease characterized by resting
95 autonomic deficits, and probed how salience network dysfunction relates to diminished
96 parasympathetic and sympathetic outflow. Our results indicate that baseline parasympathetic and
97 sympathetic tone are the product of complex, opposing intra-network nodal interactions and
98 depend on the integrity of highly tuned, lateralized salience network hubs (i.e., left ventral
99 anterior insula for parasympathetic activity and right hypothalamus/amygdala for sympathetic
100 activity).

101

102 Introduction

103 The salience network is a distributed brain system that produces emotions and monitors
104 the dynamic conditions of the body (Seeley et al., 2007). With hubs in ventral anterior insula
105 (vAI) and anterior cingulate cortex (ACC) and tight connections with ventral striatum and central
106 pattern generators including the hypothalamus, amygdala, and periaqueductal gray (PAG), the
107 salience network participates in and may coordinate autonomic nervous system (ANS)
108 regulation. During emotions, the salience network triggers visceromotor changes that disrupt
109 quiescence and move an organism from rest to action. At rest, the salience network adjusts the
110 internal milieu to meet current metabolic and motivational conditions (Benarroch, 1993;
111 Carmichael and Price, 1995; Ongur and Price, 2000; Saper, 2002; Barbas et al., 2003a; Critchley,
112 2005; Beissner et al., 2013; Critchley and Harrison, 2013). A continuous stream of sensory
113 information travels from the spinal cord through the brainstem via the lamina I spinothalamic
114 pathway and vagal afferents. This interoceptive information is then relayed to the dorsal
115 posterior insula, mid-insula, and onward to vAI, a physiological integration site that is thought to
116 represent internal feeling states that color subjective emotional experience and shape behavior
117 (Craig, 2002; Critchley, 2004; Craig, 2009; Damasio and Carvalho, 2013).

118 The salience network influences both the sympathetic and parasympathetic branches of
119 the ANS. The sympathetic ANS (SANS) responds to arousing or threatening stimuli and
120 mobilizes behavior (Saper, 2002). The parasympathetic ANS (PANS), in contrast, downregulates
121 arousal via the inhibitory influence of the vagus nerve. The vagus sends efferent signals from the
122 brain to the internal organs, reducing heart rate to a pace that is slower than that set by the
123 sinoatrial node (Carlson et al., 1992; Levy et al., 1993; Saper, 2002; Thayer and Siegle, 2002)
124 and creating a “rest and digest” state that fosters interpersonal engagement and emotional

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125 attunement (Porges, 2001). These two ANS branches appear to be asymmetrically organized in
 126 the brain. While right-lateralized (i.e., non-dominant hemisphere) neural pathways promote
 127 SANS outflow, left-lateralized (i.e., dominant hemisphere) systems facilitate PANS activity
 128 (Oppenheimer et al., 1992; Oppenheimer et al., 1996; Yoon et al., 1997; Wittling et al., 1998a;
 129 Wittling et al., 1998b; Craig, 2005; Guo et al., 2016).

130 Although previous research has examined how salience network connectivity relates to
 131 PANS activity (Guo et al., 2016), it remains unknown how within-network nodal interactions
 132 relate to individual differences in resting PANS and SANS function. The behavioral variant of
 133 frontotemporal dementia (bvFTD) is a neurodegenerative disease that targets the salience
 134 network (Seeley et al., 2007; Zhou et al., 2010) and offers a unique opportunity to examine how
 135 salience network integrity relates to ANS deficits. In bvFTD there is progressive deterioration of
 136 social behavior, empathy, and emotion (Rascovsky et al., 2007; Seeley et al., 2008; Kumfor and
 137 Piguet, 2012; Seeley et al., 2012; Barsuglia et al., 2014; Joshi et al., 2014b; Levenson et al.,
 138 2014; Mendez et al., 2014). In addition to deficits in emotion generation (Sturm et al., 2006;
 139 Sturm et al., 2008; Eckart et al., 2012), patients with bvFTD also exhibit PANS and SANS
 140 deficits at rest (Joshi et al., 2014a; Guo et al., 2016).

141 In the present study, we investigated whether specific patterns of salience network
 142 dysfunction related to resting PANS and SANS deficits. We measured baseline ANS activity in
 143 patients with bvFTD and healthy controls (HC) during a laboratory-based testing session.
 144 Participants also underwent structural magnetic resonance imaging (MRI) and task-free
 145 functional MRI (fMRI). Building on previous studies (Benarroch, 1993; Thayer and Lane, 2000;
 146 Craig, 2002; Saper, 2002; Seeley et al., 2012; Critchley and Harrison, 2013; Damasio and
 147 Carvalho, 2013), we developed a neural systems model (Figure 1A) to guide our examination of

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148 nodes and edges (i.e., connectivity between node-pairs) that are embedded in the salience
149 network and support ANS activity. We hypothesized that lateralized network impairment would
150 be associated with resting ANS deficits such that left-sided dysfunction would predict
151 diminished PANS activity whereas right-sided dysfunction would predict lower SANS activity.

152 Materials and Methods

153 *Participants*

154 We included 47 participants in the present study: 24 HC (56.7 – 79.6 years of age) and 23
155 patients with bvFTD (34.2 – 71.2 years of age) (Rascovsky et al., 2007). The HC were recruited
156 from advertisements and were free of current or previous neurological or psychiatric disorders.
157 Patients underwent an interdisciplinary team evaluation at the University of California, San
158 Francisco (UCSF) Memory and Aging Center that included a clinical interview, neurological
159 exam, functional assessment, MRI, and neuropsychological testing (Table 1). A functional
160 assessment of dementia severity was obtained using the Clinical Dementia Rating Scale (CDR)
161 (Morris, 1993). Body mass index (BMI) was calculated for all patients and for 20/21 of HC with
162 available height and weight data. Participants were not taking medications at the time of the
163 laboratory assessment (described below) that could significantly affect ANS functioning (i.e.,
164 stimulants, beta-blockers, or acetylcholinesterase inhibitors). Power calculations based on
165 previous studies of ANS dysfunction in bvFTD (Joshi et al., 2014a; Guo et al., 2016) showed
166 that an $\alpha = .05$ level test in a sample of this size had power greater than 80% to detect a difference
167 between the groups.

168 *Experimental Design and Statistical Analysis*169 *Laboratory Assessment of Autonomic Physiology*

170 *Procedure.* After informed consent, participants' physiological functioning was assessed
 171 at the Berkeley Psychophysiology Laboratory at the University of California, Berkeley
 172 (Levenson et al., 2008).

173 *Resting Baseline Autonomic Physiology.* Eleven 35-second resting baseline periods were
 174 extracted from a task in which participants viewed 11 short films; for complete details, see
 175 previous task descriptions (Goodkind et al., 2015). During these pre-film baseline periods,
 176 participants were instructed to relax and to watch an "X" on a white monitor screen.

177 *Measures.* Physiological measures were monitored continuously using a Grass Model 7
 178 or Biopac polygraph, a computer with analog-to-digital capability, and an online data acquisition
 179 and analysis software package written by Robert W. Levenson. The software computed second-
 180 by-second averages for the following measures: (1) heart rate (Beckman miniature electrodes
 181 with Redux paste were placed in a bipolar configuration on opposite sides of the participant's
 182 chest; the inter-beat interval was calculated as the interval, in milliseconds, between successive R
 183 waves); (2) respiratory sinus arrhythmia (RSA), the peak-valley method was used, which
 184 measures the time differences between the shortest inter-beat interval during inspiration and the
 185 longest inter-beat interval during expiration on each breath (Grossman et al., 1990); (3) skin
 186 conductance level (SCL), a constant-voltage device was used to pass a small voltage between
 187 Beckman regular electrodes (using an electrolyte of sodium chloride in Unibase) attached to the
 188 palmar surface of the middle phalanges of the ring and index fingers of the non-dominant hand;
 189 (4) respiration period (a pneumatic bellows was stretched around the thoracic region and the
 190 inter-cycle interval was measured in milliseconds between successive inspirations); and (5)
 191 finger temperature (a thermistor attached to the distal phalanx of the little finger of the non-
 192 dominant hand recorded temperature in degrees Fahrenheit).

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193 This array of measures was selected to sample from major ANS (cardiovascular,
 194 electrodermal, and respiratory) systems and enabled us to examine both PANS and SANS
 195 integrity. RSA is a measure of vagally-mediated, beat-to-beat variation in heart rate, an index of
 196 PANS activity (Berntson et al., 1997). RSA is closely linked to respiration, with heart rate
 197 decelerating during expiration and accelerating during inspiration. We used the peak-valley
 198 method, which quantifies the difference between the longest heart period during expiration and
 199 the shortest heart period during inspiration (Grossman et al., 1990; Grossman and Taylor, 2007).
 200 The natural logarithm of RSA (lnRSA) was used to improve proximity to a normal distribution
 201 and was used in all analyses. SCL, which increases as there is greater innervation of the eccrine
 202 sweat glands, is a relatively pure SANS measure (Critchley, 2002). Heart rate, respiration period,
 203 and temperature are influenced by both ANS branches and, therefore, were not the focus of our
 204 neuroimaging analyses.

205 Mean levels of physiological responding were computed for each 33-second pre-film
 206 baseline (one second at the beginning and end of each baseline and trial were omitted to account
 207 for measurement error in the timing of trial onset and offset) and were then averaged across all
 208 11 baseline trials. We calculated a Cronbach's alpha reliability coefficient for each channel and
 209 found high reliability for each measure across the 11 baseline periods (inter-beat interval=.99,
 210 RSA=.94, SCL=.99, respiration period=.92, and temperature=.99), which suggests that the
 211 overall baseline means were an accurate reflection of stable, trait-like baseline ANS physiology.

212 *Image Acquisition*

213 *Structural Imaging.* The majority of participants (17 HC and 22 patients) underwent
 214 research-quality MRI within close proximity of the laboratory assessment of autonomic

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215 physiology (4 months for patients and 12 months for HC). Structural images were obtained on a
 216 3.0 Tesla Siemens (Siemens, Iselin, NJ) TIM Trio scanner equipped with a 12-channel head coil
 217 located at the UCSF Neuroscience Imaging Center. Whole brain images were acquired using
 218 volumetric MPRAGE (acquisition time=8:53, sagittal orientation, a field of view of 160 x 240 x
 219 256 mm with an isotropic voxel resolution of 1 mm³, TR=2300 ms, TE=2.98 ms, TI=900 ms, flip
 220 angle=9°).

221 *Functional Imaging.* Task-free fMRI scans were also obtained in 14 HC and 17 patients
 222 with bvFTD. The 3T scanner acquired 240 task-free T2*-weighted echoplanar fMRI volumes
 223 (acquisition time=8:06, axial orientation with interleaved ordering, field of view=230 x 230 x
 224 129 mm, matrix size=92 x 92, effective voxel resolution=2.5 x 2.5 x 3.0 mm, TR=2000 ms,
 225 TE=27 ms)

226 *Image Preprocessing*

227 *Structural Imaging.* Structural T1 images were visually inspected for movement artifacts
 228 before being processed with SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>). One
 229 patient was excluded due to poor scan quality, leaving a total of 21 bvFTD and 17 HC. Within
 230 the same generative model (Ashburner and Friston, 2005), the T1-weighted images were
 231 segmented into gray and white matter using the segment program in SPM12. To guarantee
 232 voxel-wise comparability, gray matter images were normalized to Montreal Neurological
 233 Institute (MNI) space by applying 12-parameter linear transformation and non-linear warping,
 234 modulated, and smoothed with an 8 mm full-width at half-maximum Gaussian kernel.

235 *Functional Imaging.* For each fMRI scan, the first five volumes were discarded. SPM12
 236 and FSL (<http://fsl.fmrib.ox.ac.uk/fsl>) software were used for subsequent fMRI preprocessing.

237 The remaining 235 volumes were slice-time corrected, realigned to the mean functional image,
 238 and assessed for rotational and translational head motion. Volumes were next co-registered to the
 239 MP-RAGE image and then normalized to the standard MNI-152 healthy adult brain template
 240 using SPM segment, producing MNI-registered volumes with 2 mm³ isotropic resolution. These
 241 volumes were spatially smoothed with a 6 mm radius Gaussian kernel and temporally bandpass
 242 filtered in the .008-.15 Hz frequency range using fslmaths. Nuisance parameters in the
 243 preprocessed data were estimated for the cerebrospinal fluid (CSF) using a mask in the central
 244 portion of the lateral ventricles and for the white matter (WM) using a mask of the highest
 245 probability cortical WM as labeled in the FSL tissue prior mask. Additional nuisance parameters
 246 included the 3 translational and 3 rotational motion parameters, the temporal derivatives of the
 247 previous 8 terms (WM/CSF/6 motion), and the squares of the previous 16 terms (Satterthwaite et
 248 al., 2013). Any participant with a maximum relative head translation greater than 3 mm,
 249 maximum relative rotation greater than 3 degrees, or more than 10% of frames with a motion
 250 spike greater than 1 mm, were excluded from the analysis. Previous work has shown that the
 251 edges tested in the present study have moderate to good test-retest reliability with this level of
 252 head movement excluded (Guo et al., 2012) and that resting state measures are reliable when
 253 these preprocessing strategies are employed (Varikuti et al., 2017). We excluded two patients for
 254 excessive motion, leaving 14 HC and 15 patients with bvFTD. The groups (controlling for age,
 255 sex, and education) did not significantly differ on total head movement during the scan, $F(1,$
 256 $24)=1.43, p=.24, \eta_p^2=.06$.

257 *Analyses*

258 *Structural Neuroimaging Analyses.* We conducted separate whole-brain voxel-based
 259 morphometry (VBM) analyses (Bates et al., 2003) in the patients to identify brain regions in

260 which smaller gray matter volume was associated with baseline RSA and SCL deficits in bvFTD
 261 (Table 2). We chose to run the structural neuroimaging analyses in the patients only because they
 262 have significantly more atrophy than the controls in many of the regions that we expected would
 263 be related to the ANS measures and, thus, might unduly bias the analyses if we combined all of
 264 the participants. Age, sex, education were included as nuisance covariates. In a follow-up
 265 analysis, we added SCL as an additional covariate in the RSA analysis and RSA as an additional
 266 covariate in the SCL analysis, which further allowed us to examine the independence of the
 267 neural correlates of each measure. A priori significance was established at uncorrected $p < .001$.
 268 One thousand permutation analyses using combined peak and extent thresholds were run to
 269 derive a study-specific error distribution to determine the one-tailed T -threshold at $p_{FWE} < .05$,
 270 corrected for multiple comparisons (Nichols and Holmes, 2002).

271 *Functional Connectivity Neuroimaging Analyses.* Using a graph theoretical framework,
 272 we identified “connectivity clusters” that corresponded to the regions of interest (ROIs) in our
 273 model (Figure 1B). The clusters were obtained from task-free fMRI data in an independent
 274 cohort of 40 healthy older controls (20 males, all less than 66 years old) as previously described
 275 (Guo et al., 2012). In brief, we used four vAI and dorsal anterior insula (dAI) seeds, drawn from
 276 a meta-analysis of task-based fMRI studies that activated the insula (Kurth et al., 2010) to derive
 277 four connectivity maps. These four maps were entered into a full-factorial analysis, which
 278 identified brain regions with connectivity to the dAI clusters, to the vAI clusters, or to both the
 279 dAI and vAI clusters. We extracted the blood-oxygen-level dependent (BOLD) time series from
 280 21 clusters that corresponded to the ROIs in our *a priori* theoretical model (Figure 1A) and
 281 created a matrix that consisted of the connectivity strength of the edges in that model. Because
 282 the clusters are data-driven and have connectivity-based contours, they may sample a more

283 homogeneous functional signal and be better suited for matrix-based analyses than typical
284 spherical or landmark-based ROIs (Shirer et al., 2012).

285 We used previously established methods (Sturm et al., 2013) to identify key edges
286 associated with RSA and SCL. First, edges weights were *r*-to-*z* transformed, and we then ran
287 correlation analyses across the patients and controls between RSA and the connectivity strength
288 of all 210 edges in our matrix. We planned to include any regions for which the correlation
289 coefficient was greater than or equal to .20, a small to medium effect size (Cohen, 1992) and a
290 permissive inclusion threshold, as additional candidate predictor variables in subsequent
291 regression analyses. Next, we ran hierarchical regression analyses in order to determine which
292 edges were significant predictors of RSA, a conservative test of our hypotheses because edges
293 must emerge as significant predictors from a group of candidate predictor regions. In step one,
294 we entered age, sex, education, and diagnosis into the model. In step two, we used a “forward”
295 entry model to determine which edges accounted for a significant amount of variance above and
296 beyond the control variables; thus, edges that did not account for significant variance were
297 excluded from the model. In this second step, we included as predictor candidates all of the
298 edges that passed the .2 inclusion threshold from our correlation analyses. We ran three separate
299 regression analyses for ipsilateral left-hemisphere edges, ipsilateral right-hemisphere edges, and
300 edges that crossed to the contralateral hemisphere (i.e., left to right or right to left) to minimize
301 potential collinearity between homologous regions. We also examined our models to confirm
302 that there was only weak multicollinearity among variables (variance inflation factor<4). We
303 next repeated this entire process to identify edges that were significant predictors of baseline
304 SCL. For each regression, we visually inspected the histogram and P-P plot of the standardized
305 residuals to ensure that the error terms were normally distributed. The plots showed that the

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306 points generally followed the normal (diagonal) line with no outliers or strong deviations,
307 indicating that the assumptions of the regression models were met.

308 To ensure that any associations between functional connectivity and ANS physiology
309 were not due to atrophy, we conducted another set of hierarchical regression analyses for RSA
310 and SCL. From the structural scans, we extracted the total gray matter volume from each ROI.
311 Here, in addition to the other nuisance covariates (age, sex, education, and diagnosis), we also
312 included the mean ROI volumes for each of the edges (i.e., the mean volume of each node that
313 comprised the relevant edges) that had entered the original forward-entry regression models in
314 step one. In step two, we included the connectivity strength of the edges that had entered the
315 models in our original analyses.

316 We anticipated that any associations that we detected between ANS activity and
317 functional connectivity would reflect a general relationship that is not specific to either
318 diagnosis. To confirm that this was the case, we repeated the final regression models (for
319 ipsilateral left-hemisphere edges, ipsilateral right-hemisphere edges, and edges that crossed to
320 the contralateral hemisphere) for RSA and SCL in each diagnosis separately. Here, we included
321 age, sex, and education as nuisance covariates in step one. In step two, we entered the edges that
322 had explained a significant portion of the variance in the forward-entry regression models we had
323 conducted across the sample. Although each diagnostic group was much smaller than the total
324 sample and, thus, our power was substantially reduced in these analyses, our aim was to
325 investigate whether the effect sizes of any the associations between functional connectivity and
326 ANS activity that we detected across the sample were comparable in each of the diagnostic
327 groups when examined separately.

328 In a separate set of regressions, we examined whether the mean connectivity strength of
 329 the edges that entered the regression RSA and SCL models were lower in bvFTD compared to
 330 HC. In these analyses, the independent variable was diagnosis (bvFTD or HC), and the
 331 covariates included age, sex, and years of education.

332 Results

333 *Smaller left vAI volume and lower vAI – ACC connectivity are associated with lower baseline*
 334 *PANS activity*

335 In bvFTD, lower RSA was related to atrophy in a large cluster within left vAI, among
 336 other regions (Table 3 and Figure 2A). When we also controlled for SCL in this RSA analysis,
 337 the results remained largely unchanged though some regions that were more weakly associated
 338 with RSA no longer remained significant (Table 3 and Figure 2B). Forward-entry hierarchical
 339 regression analyses across the bvFTD and HC groups determined that weaker functional
 340 connectivity in bilateral vAI – ACC edges, including left vAI – left ACC (2–5), left vAI – right
 341 ACC (2–16), and right vAI – right ACC (13–15), was associated with lower baseline RSA
 342 (Table 4 and Figure 2C). The functional connectivity results remained significant after atrophy
 343 correction. When we repeated the original regression analyses in each diagnosis separately, there
 344 were similar associations between RSA and the functional connectivity measures (Figure 4-1).
 345 Patients with bvFTD had significantly lower connectivity strength than the HC in the right vAI –
 346 right ACC (13–15) and left ACC – right amygdala (6–18) edges (Table 5). These findings
 347 indicate that structural and functional deterioration of vAI (left > right) and its connections with
 348 ACC are associated with a loss of basal parasympathetic tone as measured by RSA.

349 *Stronger connectivity in ACC – hypothalamus/amygdala edges relates to lower baseline PANS*
 350 *activity*

351 Although lower RSA was associated with weaker vAI – ACC connectivity, the regression
 352 analyses also revealed that lower RSA was associated with stronger connectivity in other edges.
 353 Most notably, stronger connections between bilateral ACC and predominantly right-sided
 354 hypothalamus/amygdala edges were associated with lower RSA (Table 4 and Figure 2C). This
 355 pattern was not mirrored in the VBM analyses in that there were no regions where larger volume
 356 was associated with lower RSA. All of the functional connectivity results held with atrophy
 357 correction, with the exception of the right pregenual ACC – right hypothalamus ($p=.07$) and right
 358 vAI – right hypothalamus ($p=.30$) edges. These results suggest that RSA depends on both
 359 functional integrity of vAI – ACC edges and suppressed connectivity in ACC – hypothalamus
 360 and ACC – amygdala edges (particularly in the right hemisphere), regions that appear to inhibit
 361 PANS activity, perhaps by promoting SANS outflow.

362 *Stronger connectivity in ACC – hypothalamus/amygdala edges relates to higher SANS activity*

363 If the hypothalamus and amygdala promote SANS activity as suggested by the RSA
 364 analyses, then we would expect that preserved volume and connectivity in these regions would
 365 be associated with higher SCL. Consistent with this framework, larger volume in left inferior
 366 temporal gyrus and left hypothalamus as well as right hypothalamus, amygdala and
 367 periaqueductal gray (at a more permissive threshold of $p<.005$) was associated with higher SCL
 368 (Table 3 and Figure 3A). Furthermore, when we also controlled for RSA in this SCL analysis,
 369 the results remained largely unchanged though some regions that were more weakly associated
 370 with SCL no longer remained significant (Table 3 and Figure 3B). Stronger bilateral ACC –

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hypothalamus connectivity was also associated with higher baseline SCL (Table 4 and Figure 3C). Although there were no regions for which larger volume was associated with lower SCL, stronger connectivity in bilateral dAI – PAG and left anterior midcingulate cortex (aMCC) – right hypothalamus edges did relate to lower SCL (Table 4 and Figure 3C). All functional connectivity results held with atrophy correction. When we repeated the original regression analyses in each diagnosis separately, there were similar associations between SCL and the functional connectivity measures (Figure 4-1). Taken together, these findings suggest that the right hypothalamus in particular is a key hub in SANS outflow and that atrophy and diminished connectivity in right hypothalamus/amygdala edges impede SCL. Patients with bvFTD had significantly lower connectivity strength than the HC in the left ACC – right hypothalamus (6–19), right ACC – right amygdala (16–18), right ACC – left ACC (17–5), right dAI – PAG (11–21), and left aMCC – right hypothalamus (4–19) edges (Table 5). Visual inspection of the data confirmed that significant associations that emerged between the functional connectivity measures and ANS activity were not driven by group effects (Figure 4).

Discussion

The salience network coordinates the parasympathetic and sympathetic branches of the ANS (Benarroch, 1993; Ongur and Price, 2000; Thayer and Lane, 2000; Saper, 2002; Seeley et al., 2007; Beissner et al., 2013; Critchley and Harrison, 2013). This system enables the brain to trigger changes in the periphery and to receive continuous feedback about the physiological conditions of the body (Craig, 2002; Seeley et al., 2012; Critchley and Harrison, 2013). Previous research has revealed cerebral hemispheric asymmetry in PANS and SANS neural systems organization (Oppenheimer et al., 1992; Craig, 2005). Whereas the left hemisphere is essential for PANS functioning (Wittling et al., 1998a; Guo et al., 2016), the right hemisphere plays a

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dominant role in SANS activation (Yoon et al., 1997; Wittling et al., 1998b). In keeping with this anatomical framework, our results suggest that healthy PANS and SANS activities are the product of complex, opposing intra-network nodal interactions. We found that the structural and functional integrity of specific hubs that have been identified in prior studies—left vAI for PANS and right hypothalamus/amygdala for SANS (Xavier et al., 2013; Guo et al., 2016)—were critical for maintaining resting ANS outflow. Although the left vAI and right hypothalamus/amygdala hubs were lateralized and located in the predicted hemispheres, they had connections with ipsilateral and contralateral network nodes that were also integral for baseline ANS activity. While ipsilateral pathways may facilitate within-hemisphere generation of PANS or SANS activity, contralateral projections may foster communication between hemispheres and enable system-level integration of PANS and SANS information. A distributed, bilateral ANS network that is anchored by asymmetric hubs may provide an efficient physiological system in which opposing PANS and SANS influences remain in a dynamic equilibrium at rest but can generate emotional reactions when needed.

RSA depends on strong vAI – ACC integrity and weak ACC – hypothalamus/amygdala connectivity

Our analyses revealed a constellation of nodes and edges that were associated with resting RSA. Consistent with previous findings, vAI and pregenual ACC emerged as key hubs of PANS control (Oppenheimer et al., 1996; Gianaros et al., 2004; Thayer et al., 2012; Allen et al., 2015; Guo et al., 2016; Jennings et al., 2016). Left vAI volume was positively associated with RSA in the structural neuroimaging analyses, and stronger connectivity in left vAI edges was also associated with higher RSA. vAI and pregenual ACC have tight reciprocal connections (Mesulam and Mufson, 1982; Carmichael and Price, 1996) and send projections to ANS

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417 brainstem nuclei including the nucleus ambiguus and dorsal motor nucleus of the vagus (Shipley,
418 1982; Hurley et al., 1991), a system that may promote the relay of PANS commands from
419 cortical and subcortical hubs to peripheral organs such as the heart (Gatti et al., 1996).

420 In addition to edges in which stronger connectivity was associated with higher RSA,
421 patients with weaker ACC – hypothalamus and ACC – amygdala connectivity had higher RSA.
422 Interestingly, stronger connectivity in ACC – hypothalamus and ACC – amygdala edges was
423 also associated with higher SCL, suggesting that the hypothalamus and amygdala (particularly in
424 the right hemisphere) are central pattern generators essential for SANS outflow (Barbas and De
425 Olmos, 1990; Laine et al., 2009; Xavier et al., 2013). Direct connections from ACC to the
426 intermediolateral cell column (Bacon and Smith, 1993), or indirect connections through
427 hypothalamus or amygdala (Saper et al., 1976; ter Horst et al., 1984; Barbas et al., 2003b), may
428 promote SANS outflow. Therefore, higher connectivity between these regions and ACC may
429 impede PANS activity by stimulating SANS outflow, consistent with prior studies showing an
430 antagonistic relation between PANS and SANS activity (Levy, 1990; Saku et al., 2014). Our
431 results suggest that RSA depends not only on strong connectivity in vAI – ACC, which promotes
432 vagal tone, but also on relatively weak, or suppressed, connectivity in ACC –
433 hypothalamus/amygdala, connections that encourage sympathetic outflow.

434 *SCL depends on ACC – hypothalamus/amygdala integrity and weak dAI – PAG connectivity*

435 Together with ACC, the amygdala and hypothalamus are integral SANS hubs (Bandler
436 and Carrive, 1988; An et al., 1998; Ongur et al., 1998; Price, 1999; Ongur and Price, 2000). Our
437 results indicate that stronger pregenua ACC – hypothalamus/amygdala connectivity was
438 associated with higher SCL. Larger volume in inferior temporal gyrus, hypothalamus, amygdala,

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439 and periaqueductal gray, among other regions, also predicted greater SCL activity. The integrity
 440 of pregenual ACC and its direct projections with hypothalamus and amygdala, therefore, appears
 441 to be essential for SANS outflow (Barbas and De Olmos, 1990; Davis and Whalen, 2001;
 442 Ghashghaei and Barbas, 2002; Laine et al., 2009).

443 Like RSA, SCL depended on stronger connectivity in some edges but weaker
 444 connectivity in others. Lower bilateral dAI – PAG and left aMCC – right hypothalamus
 445 connectivity was associated with higher SANS tone. Both aMCC and dAI are key structures in
 446 an inhibitory control system that constrains cognition and behavior and may also downregulate
 447 physiological arousal (Aron et al., 2004; Nee et al., 2007; Touroutoglou et al., 2012; Enriquez-
 448 Geppert et al., 2013; Hoffstaedter et al., 2014). Through connections with lateral frontoparietal
 449 task control networks (Mesulam and Mufson, 1982; Mufson and Mesulam, 1982), dAI plays a
 450 central role in response inhibition and emotion suppression (Aron, 2007; Giuliani et al., 2011).
 451 The structural and functional integrity of aMCC has been associated with greater heart rate
 452 variability (Critchley et al., 2003; Winkelman et al., 2016), and connectivity in this region,
 453 therefore, may contribute to dampening, rather than inducing physiological arousal. Although we
 454 were unable to examine substructures within our subcortical ROIs, this hypothesis would be
 455 especially compelling if the connectivity strength from our PAG and hypothalamus ROIs
 456 primarily captured the activity of their PANS-relevant subregions (Bandler and Shipley, 1994; da
 457 Silva et al., 2003) (Figure 5). Weakened connectivity in a PANS-mediated visceromotor braking
 458 system, therefore, may facilitate SANS activity. In bvFTD, atrophy and connectivity disruption
 459 involving both PANS and SANS structures likely resulted in a net loss of RSA and SCL activity
 460 despite altered intra-network nodal interactions.

Limitations

462 There are several limitations of the present study that should be considered. First, the HC
463 were older than the patients with bvFTD. Given that RSA and SCL decline in normal aging
464 (Barontini et al., 1997; Masi et al., 2007), the age distribution of our sample would work against
465 our hypothesis and make it more difficult for us to detect ANS impairment in the younger
466 clinical group. Furthermore, we took several additional steps to mitigate the potential impact of
467 age on our results: (1) our primary analyses were regression analyses rather than group
468 comparisons, which allowed us to investigate how brain volume and functional connectivity
469 related to ANS activity across the diagnostic groups, (2) we included age as a covariate in all
470 analyses, (3) we conducted a follow-up analysis on ANS activity in a subgroup of patients who
471 were age-matched and continued to find PANS and SANS deficits in bvFTD, a pattern that is
472 consistent with previous studies (Joshi et al., 2014a; Guo et al., 2016). We also found that
473 patients had faster baseline respiration rates, an alteration that may also reflect disruption of
474 vagal pathways (Carlson et al., 1992; Critchley, 2002; Rybak et al., 2004). Given that our sample
475 size was relatively small, additional studies are needed to detect the more subtle relationships
476 that might exist between functional connectivity and ANS outflow. Larger studies of bvFTD will
477 also be critical for elucidating whether RSA deficits relate to the alterations in respiration that we
478 detected. Second, our study was not able to examine the functional connectivity of many relevant
479 ANS brainstem nuclei, and many of our subcortical ROIs could have been deconstructed further
480 into anatomically meaningful subregions with specific PANS and SANS roles. The
481 hypothalamus and PAG, for example, can be divided into subregions that receive distinct
482 projections from ACC and vAI and play different roles in PANS and SANS (Bandler and
483 Shipley, 1994; Price, 1999). Because of this limitation, we may have failed to detect important
484 associations between these subregions and our ANS measures. Future studies that are able to

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485 subdivide these small structures into even finer parcels will continue to elucidate the neural
486 architecture of ANS functioning. Third, whereas our PANS measure, RSA, was a cardiovascular
487 measure, our SANS measure, SCL, was an electrodermal measure. Future studies that utilize
488 cardiovascular measures of SANS activity, such as impedance cardiography, could help to
489 determine whether all aspects of SANS activity are similarly disrupted in bvFTD or whether the
490 SANS impairment is specific to electrodermal outflow. Given that SCL is a cholinergic, rather
491 than an adrenergic, SANS measure, it is also possible that cholinergic dysfunction in bvFTD may
492 underlie both the RSA and SCL deficits that we detected. Whether the adrenergic system is also
493 altered in bvFTD will need to be addressed in future studies.

494 *Conclusion*

495 Although a single distributed neural network supports ANS physiology, opposing PANS
496 and SANS subsystems within this network play distinct roles in homeostasis maintenance. Our
497 results suggest that highly calibrated connections within the PANS and SANS subnetworks
498 promote ANS outflow. Disruption of these subsystems in bvFTD may tip the autonomic balance
499 and alter resting physiology as well as emotional responding. These findings may have wider
500 implications for the study of psychiatric conditions with alterations in emotion and behavior.

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- 736

737

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744

745

Table 1

Participant characteristics classified by diagnostic group. Means (*M*) and standard deviations (*SD*) are listed for each group unless otherwise noted. Neuropsychological testing included assessment of verbal and visual episodic memory, executive function (e.g., set-shifting, working memory, and fluency), language, and visuospatial functioning. A total of 19/23 patients and 17/24 HC completed neuropsychological testing in close proximity (within 4 months for patients and 12 months for the HC) to the laboratory assessment. The CDR Total and Sum of the Boxes were computed for each participant with higher scores indicating greater impairment. bvFTD= behavioral variant frontotemporal dementia, BMI= Body Mass Index, CDR Total= Clinical Dementia Rating Total score, CDR-SB= Clinical Dementia Rating Sum of Boxes, HC= healthy controls, and MMSE= Mini-Mental State Examination. † The HC received the California Verbal Learning Test-II (16-word list) instead of the Short Form. Their performance on the 20-minute delay was also in the average range ($M= 13.6$, $SD= 2.1$). We used analysis of variance and chi-square tests, when appropriate, to examine group differences. Partial eta squared (η_p^2) is provided as a measure of effect size.

	<i>bvFTD</i> <i>M(SD)</i>	<i>HC</i> <i>M(SD)</i>	<i>p</i>	η_p^2
N	23	24		
Age	58.4 (8.4)	67.9 (5.4)	<.001	.31
Sex: % Female	30.4	54.2	.10	
Education	15.7 (2.9)	17.6 (2.3)	.02	.12
Handedness: % Right-handed	100.0	91.7	.16	
BMI	32.2 (29.1)	25.8 (12.3)	.37	.02
CDR Total	1.2 (0.6)	0.0 (0.0)	<.001	.72

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CDR-SB	7.2 (2.8)	0.0 (0.0)	<.001	.77
MMSE	23.9 (5.2)	29.6 (0.6)	<.001	.38
California Verbal Learning Test- Short Form 10-Minute Recall (/9)	3.8 (2.3)	†		
Benson Figure Copy 10-Minute Recall (/17)	6.8 (4.4)	11.4 (2.6)	.001	.29
Modified Trails (correct lines per minute)	13.9 (13.0)	39.6 (12.1)	<.001	.53
Modified Trails Errors	2.4 (2.4)	0.2 (0.4)	.001	.31
Phonemic Fluency (# correct in 60 seconds)	5.5 (3.8)	19.2 (4.3)	<.001	.76
Semantic Fluency (# correct in 60 seconds)	9.1 (4.7)	24.0 (5.3)	<.001	.70
Design Fluency Correct (# correct in 60 seconds)	4.8 (3.3)	11.8 (2.8)	<.001	.58
Design Fluency Repetitions	7.3 (6.3)	1.8 (2.4)	.001	.26
Digits Backward	3.2 (0.9)	6.0 (1.4)	<.001	.61
Benson Figure Copy (/17)	13.8 (2.1)	15.3 (1.0)	.015	.16
Calculations (/5)	3.3 (1.1)	4.9 (0.2)	<.001	.54
Boston Naming Test Spontaneous Correct (/15)	11.8 (3.1)	14.6 (0.7)	<.001	.30
Peabody Picture Vocabulary Test (/16)	13.7 (3.3)	15.7 (0.6)	.025	.15

761

762 Table 2

763 *Resting baseline physiological levels.* Analyses of covariance (controlling for age, sex, and
 764 education) found that patients with bvFTD (n=22) had significantly lower respiratory sinus
 765 arrhythmia, lower skin conductance level, and shorter respiration period than the healthy controls
 766 (n=22). When we added additional covariates that might influence RSA (i.e., resting inter-beat
 767 interval, resting respiration period, and body mass index) to the model (while also controlling for
 768 education, sex, and age), patients continued to have lower RSA, $F(1, 33)= 469, p= .038, \eta_p^2= .13$.
 769 For SCL, although including resting inter-beat interval, resting respiration period, and body mass
 770 index as additional covariates caused the difference to fall to trend levels, the pattern of results
 771 was in the expected direction, with patients having lower SCL than controls, $F(1, 32)= 2.82, p<$
 772 $.11, \eta_p^2= .08$. To examine whether the results of the original model (controlling for age, sex, and
 773 education) held in a smaller, age-matched sample, we removed patients under age 58 (n=6) and
 774 healthy controls over age 70 (n=8). In this subset of participants (17 bvFTD and 15 HC), the
 775 patients and controls did not differ in age, $F(1,31)=3.2, p=.09, \eta_p^2=.09$. In this smaller sample, the
 776 group differences in baseline autonomic activity remained significant. Compared to healthy
 777 controls, patients with bvFTD had lower RSA, $F(1,27)=5.6, p=.03, \eta_p^2=.17$, lower SCL,
 778 $F(1,27)=4.2, p= .05, \eta_p^2=.14$, and shorter respiration period, $F(1,27)=8.1, p= .008, \eta_p^2=.23$. Means
 779 (M) and standard deviations (SD) are reported. Partial eta squared (η_p^2) is provided as a measure
 780 of effect size. * indicates significant differences at $p< .05$ in the first model described above.

<i>bvFTD</i>	<i>Healthy</i>			
<i>M(SD)</i>	<i>Controls</i>	<i>F</i>	<i>p</i>	η_p^2
	<i>M(SD)</i>			

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Inter-beat interval (ms)	906.6 (156.74)	981.9 (133.9)	0.3	.57	.01
Respiratory sinus arrhythmia (ms)*	39.1 (22.9)	62.9 (55.3)	10.0	.003	.20
Skin conductance level (μmhos)*	2.0 (0.9)	2.9 (1.7)	4.6	.037	.10
Respiration period (ms)*	4035.6 (915.5)	4750.3 (946.6)	9.4	.004	.19
Finger temperature (°F)	80.7 (5.5)	80.5 (5.6)	0.0	.97	.00

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Table 3

Anatomical correlates of baseline PANS and SANS activity. Whole-brain VBM analyses in patients with bvFTD (controlling for age, sex, and education) revealed that atrophy in many ANS network nodes was associated with lower baseline RSA (n=21) and SCL (n=20). Montreal Neurological Institute coordinates (x, y, z) given for maximum *T*-score for the cluster (cluster size > 150 mm³). Results are significant at $p < .001$, uncorrected. † denotes significance at $p_{\text{FWE}} < .05$. To identify the independent neural correlates of PANS and SANS activity, we conducted follow-up VBM analyses when controlling for the opposing autonomic measure (i.e., including SCL as an additional covariate in the RSA VBM analysis and SCL as an additional covariate in the RSA VBM analysis). * denotes significance at $p < .001$, uncorrected, when also controlling for the opposing autonomic measure.

<i>Anatomical Region</i>	<i>Cluster Volume (mm³)</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>Maximum T-score</i>	<i>β</i>
RSA						
Left ventral anterior insula*	1312	-41	12	-15	5.41	.79
Left inferior temporal lobe*	448	-32	2	-36	4.96	.59
Right parahippocampal gyrus	320	15	11	-30	4.50	.63
Left parahippocampal gyrus*	168	-14	8	-26	4.28	.68
SCL						
Left inferior temporal gyrus†*	6120	-51	-21	-27	6.57	.77
Left temporal pole*	1528	-33	9	-50	5.02	.72
Right fusiform gyrus*	1200	27	-15	-41	5.05	.69
Left precentral gyrus	1160	-41	-18	59	4.31	.75
Left dorsal mid-insula*	1088	-36	14	15	7.08	.61
Left orbitofrontal cortex*	1080	-21	18	-16	4.71	.65
Left orbitofrontal cortex*	1080	-18	47	-21	5.34	.67
Right orbitofrontal cortex*	912	26	21	-11	5.16	.54
Right frontal pole*	880	8	71	14	5.77	.81
Right frontal pole	776	-15	69	-11	5.38	.67
Left parahippocampal gyrus*	712	-11	-8	-35	5.60	.79

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Right middle frontal gyrus*	672	50	14	51	6.20	.89
Left superior frontal gyrus	600	-17	41	51	4.65	.81
Right postcentral gyrus	584	23	-30	74	4.25	.76
Right precentral gyrus*	496	44	-20	60	4.30	.69
Left precuneus	424	-17	-41	71	4.94	.70
Left frontal pole*	424	-38	56	9	4.30	.66
Left hypothalamus	424	-8	-5	-9	4.14	.60
Left fusiform gyrus	416	-33	-17	-44	4.17	.73
Right gyrus rectus	352	9	33	-17	4.16	.54
Right precentral gyrus	320	35	-8	62	4.75	.80
Left fusiform gyrus	304	51	-11	-29	4.33	.60
Left inferior parietal lobe	280	-47	-50	54	4.29	.73
Right superior frontal gyrus*	280	23	57	36	5.16	.67
Left precentral gyrus*	264	-32	-9	63	4.33	.77
Right cerebellum*	232	35	-50	-45	4.02	.50
Left pars triangularis	200	-33	33	3	4.09	.75
Right inferior parietal lobe	192	48	-42	59	4.38	.66
Left supplementary motor area	160	-9	8	65	4.61	.63

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798 Table 4

799 *Node-pair connections (i.e. edges) that explained a significant portion of variance in RSA and*
800 *SCL in the regression analyses.* Forward-entry hierarchical regression analyses in 15 patients
801 with bvFTD and 13 healthy controls (controlling for age, sex, education, and diagnosis) were
802 used to determine which edges were significant predictors of baseline PANS and SANS. Edges
803 with positive and negative associations with RSA and SCL entered the models, suggesting that a
804 combination of strong and weak functional connectivity in the ANS network is necessary for
805 resting physiological activity. † denotes edge that lost significance when controlling for mean
806 resting respiration period and inter-beat interval. * denotes edges that lost significance when
807 controlling for the mean gray matter volume of the nodes in that edge.

<i>Edge Category</i>	<i>Edge Label</i>	<i>Zero-order Correlation</i>	<i>β</i>	<i>R^2 Change</i>	<i>p-value of F Change</i>
RSA					
<i>Positive Correlation</i>					
Left vAI –	2–5	.41	.48	.22	.002
Left ACC					
Left vAI –	2–16	.33	.51	.14	.01
Right ACC †					
Right vAI –	13–15	.29	.83	.12	.03
Right ACC					

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<i>Negative Correlation</i>					
Left ACC –	7–9	-.57	-.56	.20	.01
Left Hypothalamus					
Left ACC –	7–19	-.57	-.52	.30	.001
Right Hypothalamus					
Right ACC –	16–19	-.33	-.37	.12	.01
Right Hypothalamus†					
Right vAI1 –	12–13	-.32	-.61	.09	.04
Right vAI2					
Right ACC –	17–19	-.30	-.43	.06	.04
Right Hypothalamus*					
Right vAI –	13–19	-.26	.11	.21	.01
Right Hypothalamus†*					
Right vAI –	12–17	-.25	-.32	.06	.01
Right ACC†					
Left ACC –	6–18	-.22	-.42	.09	.02
Right Amygdala†					
SCL					
<i>Positive Correlation</i>					
Left ACC –	6–19	.31	.65	.14	.02
Right Hypothalamus					
Right ACC –	16–18	.23	.38	.08	.04
Right Amygdala					
<i>Negative Correlation</i>					
Left dAI –	1–21	-.37	-.54	.25	.003

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PAG					
Right vAI1 –	12–13	-.31	-.39	.10	.03
Right vAI2					
Right ACC –	17–5	-.30	-.40	.12	.01
Left ACC					
Right dAI –	11–21	-.28	-.71	.25	.003
PAG					
Left aMCC –	4–19	-.20	-.59	.16	.02
Right Hypothalamus					

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Table 5

Edge weight connectivity strength in bvFTD versus healthy controls. Mean connectivity strengths of the edges that entered the RSA and SCL regression models for bvFTD (n=15) and healthy control (n=14) groups.

Edge Category	Edge Label	bvFTD M (SD)	Healthy Controls M (SD)	T	p
RSA					
<i>Positive Correlation</i>					
Left vAI –	2–5	.40	.46	-1.17	.25
Left ACC		(.28)	(.31)		
Left vAI –	2–16	.41	.49	-0.77	.45
Right ACC		(.29)	(.24)		
Right vAI –	13–15	.44	.51	-2.42	.02
Right ACC		(.29)	(.28)		
<i>Negative Correlation</i>					
Left ACC –	7–9	.17	.14	-0.01	.99
Left Hypothalamus		(.31)	.25)		
Left ACC –	7–19	.14	.20	0.08	.94
Right Hypothalamus		(.25)	(.17)		
Right ACC –	16–19	.13	.32	1.43	.17
Right Hypothalamus		(.24)	(.19)		

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	Right vAI1 –	12–13	.66	.66	-0.17	.87
	Right vAI2		(.26)	(.25)		
	Right ACC –	17–19	.12	.28	0.22	.83
	Right Hypothalamus		(.26)	(.18)		
	Right vAI –	13–19	.20	.35	0.30	.77
	Right Hypothalamus		(.24)	(.21)		
	Right vAI –	12–17	.31	.33	-0.73	.47
	Right ACC		(.28)	(.22)		
	Left ACC –	6–18	.20	.41	-2.28	.03
	Right Amygdala		(.24)	(.34)		
SCL						
	<i>Positive Correlation</i>					
	Left ACC –	6–19	.11	.37	-2.04	.05
	Right Hypothalamus		(.23)	(.17)		
	Right ACC –	16–18	.18	.39	-2.14	.04
	Right Amygdala		(.18)	(.33)		
	<i>Negative Correlation</i>					
	Left dAI –	1–21	.06	.12	-1.04	.31
	PAG		(.27)	(.32)		
	Right vAI1 –	12–13	.66	.66	-0.17	.86
	Right vAI2		(.26)	(.25)		
	Right ACC –	17–5	.47	.52	-2.21	.04
	Left ACC		(.19)	(.25)		
	Right dAI –	11–21	-.05	.15	-2.31	.03
	PAG		(.22)	(.24)		

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Left aMCC –	4–19	.14	.36	-2.24	.04
Right Hypothalamus		(.25)	(.22)		

814

815 Legends

816 Figure 1

817 *Anatomical framework of autonomic functioning and relevant ROIs.* (A) Building on previous
 818 studies, we developed a lateralized schematic of parasympathetic autonomic nervous system
 819 (PANS) and sympathetic autonomic nervous system (SANS) functioning. The salience network
 820 is anchored by hubs in anterior insula (AI) and anterior cingulate cortex (ACC) and has tight
 821 connections with central pattern generators including the amygdala, hypothalamus, and
 822 periaqueductal gray. Although this framework does not include many brainstem regions that are
 823 also integral for ANS activity (e.g., nucleus of the solitary tract, parabrachial nucleus, nucleus
 824 ambiguus, dorsal motor nucleus of the vagus, and rostral ventrolateral medulla, among others), it
 825 does include critical cortical and subcortical regions that can be measured with neuroimaging
 826 techniques. Thus, this represents a simplified yet testable conceptualization of the neural system
 827 that supports resting physiological activity as well as phasic emotional reactions. (B) We
 828 extracted the BOLD time series from 21 ROIs that pertained to our neuroanatomical model of
 829 ANS functioning. Connectivity strength between each node-pair (or edge) was calculated by
 830 correlating the BOLD time series of each ROI with the BOLD time series of every other ROI,
 831 which provided us with a matrix of 210 edges to correlate with measures of baseline RSA and
 832 SCL. The ROIs were functionally connected to the insula and were obtained from task-free fMRI
 833 data in an independent cohort of healthy older controls. These ROIs (with the numerical labels
 834 that we assigned to them denoted in parentheses) included: left dorsal AI (1), right dorsal AI
 835 (11), left ventral AI node 1 (2), right ventral AI node 1 (12), left ventral AI node 2 (3), right
 836 ventral AI node 2 (13), left anterior midcingulate cortex (4), right anterior midcingulate cortex
 837 (14), left pregenual ACC node 1 (5), right pregenual ACC node 1 (15), left pregenual ACC node

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838 2 (6), right pregenual ACC node 2 (16), left subgenual ACC (7), right subgenual ACC (17), left
 839 amygdala (8), right amygdala (18), left hypothalamus (9), right hypothalamus (19), left thalamus
 840 (10), right thalamus (20), periaqueductal gray (21). AI = anterior insula, ACC = anterior
 841 cingulate cortex, aMCC = anterior midcingulate cortex, Amy = amygdala, dAI = dorsal anterior
 842 insula, Hyp = hypothalamus, PAG = periaqueductal gray, Thal = thalamus, and vAI = ventral
 843 anterior insula.

844 Figure 2

845 *Baseline PANS activity is determined by the strength of certain salience network connections*
 846 *and the suppression of others.* (A) Atrophy in left vAI was associated with lower RSA at $p <$
 847 .001, uncorrected (controlling for age, sex, and education) in 21 patients with bvFTD. Cyan
 848 represents T -scores at $p <$.001, uncorrected ($T >$ 3.69), and green represents t -scores at $p <$.005,
 849 uncorrected ($T >$ 2.92). (B) We conducted a follow-up VBM analysis of RSA in which we added
 850 SCL as an additional covariate to the model. The results remained largely unchanged though
 851 some weaker clusters no longer remained significant. Cyan represents T -scores at $p <$.001,
 852 uncorrected ($T >$ 3.79), and green represents T -scores at $p <$.005, uncorrected ($T >$ 2.98). (C) The
 853 fMRI analyses revealed that lower baseline PANS activity was associated with lower vFI – ACC
 854 connectivity and higher connectivity primarily in ACC – hypothalamus/amygdala. Line
 855 thickness is scaled to reflect the percentage of variance that each edge explained (i.e., R^2 change,
 856 which ranged from .06 to .30) in the hierarchical regression model. Statistical maps are
 857 superimposed on the Montreal Neurological Institute template brain.

858 Figure 3

859 *Baseline SANS activity is determined by the strength of certain salience network connections and*
 860 *the suppression of others.* (A) Atrophy in inferior temporal gyrus, dorsal mid-insula, and
 861 hypothalamus was associated with lower SCL at $p < .001$, uncorrected (controlling for age, sex,
 862 and education) in 20 patients with bvFTD. At more permissive thresholds ($p < .005$, uncorrected),
 863 smaller volume in the amygdala and PAG was also associated with lower SCL. The inferior
 864 temporal gyrus was the only cluster that survived permutation analysis, $p_{FWE} < .05$. Cyan
 865 represents T -scores at $p < .001$, uncorrected ($T > 3.73$), and green represents t -scores at $p < .005$,
 866 uncorrected ($T > 2.95$). (B) We conducted a follow-up VBM analysis of SCL in which we added
 867 RSA as an additional covariate to the model. The results remained largely unchanged though
 868 some weaker clusters no longer remained significant. Blue represents T -scores at $p < .001$,
 869 uncorrected ($T > 3.79$), and green represents T -scores at $p < .005$, uncorrected ($T > 2.98$). (C)
 870 Baseline SANS deficits were associated with lower connectivity in right amygdala/hypothalamus
 871 edges and higher connectivity primarily in bilateral dAI – PAG edges. Line thickness is scaled to
 872 reflect the percentage of variance that each edge explained (i.e., R^2 change, which ranged from
 873 .08 to 25) in the hierarchical regression model. Statistical maps are superimposed on the
 874 Montreal Neurological Institute template brain.

875 Figure 4

876 *Regression Plots for the Functional Imaging Analyses.* Partial residual plots for the four edges
 877 that explained the greatest percentage of variance (R^2 change) in RSA and SCL (controlling for
 878 age, sex, education, and diagnosis). Higher resting RSA was associated with (A) greater left vAI
 879 – left ACC (edge 2–5) and (B) lower left ACC – right hypothalamus (edge 7–19) functional
 880 connectivity. Higher SCL was associated with (C) greater left ACC – right hypothalamus (edge
 881 6–19) and (D) lower right dAI – PAG (edge 11–21) functional connectivity. Given that we

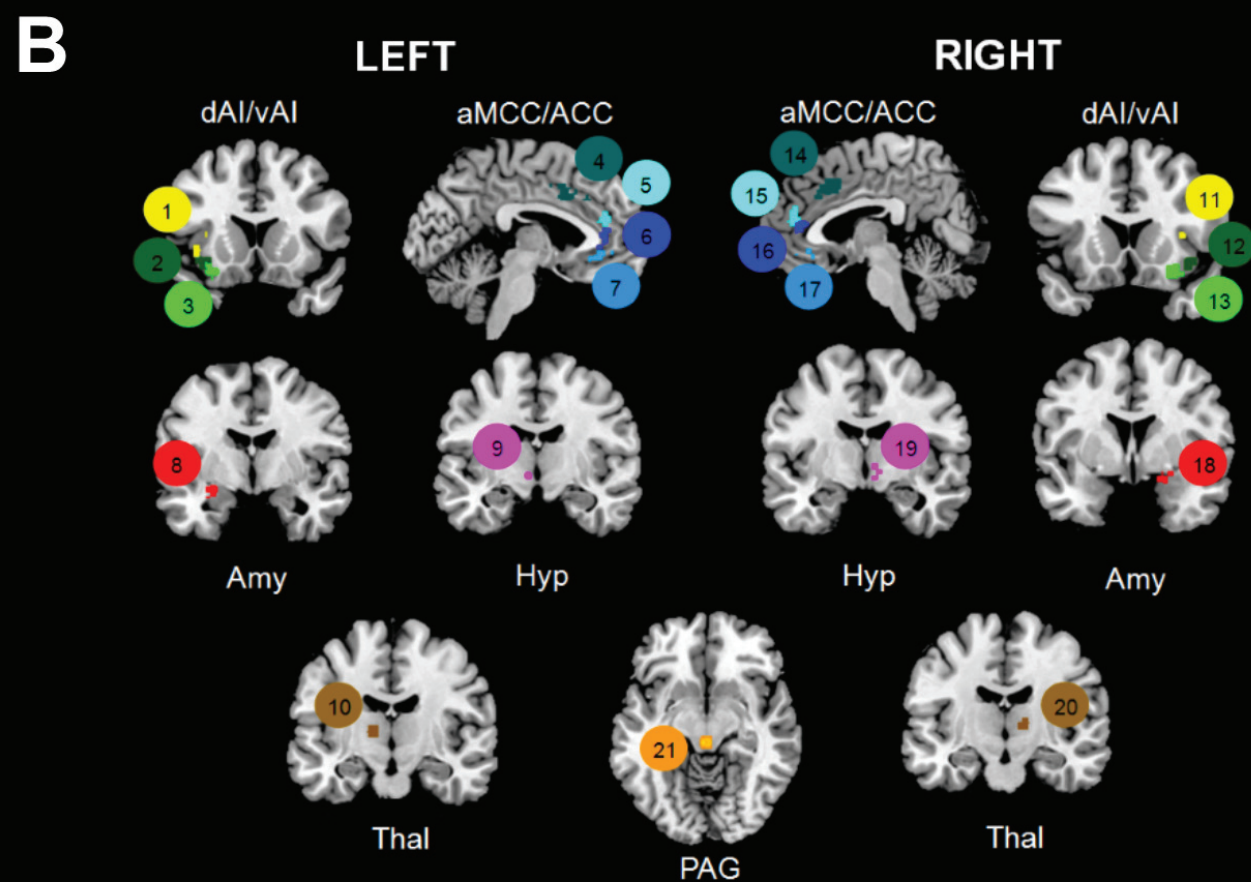
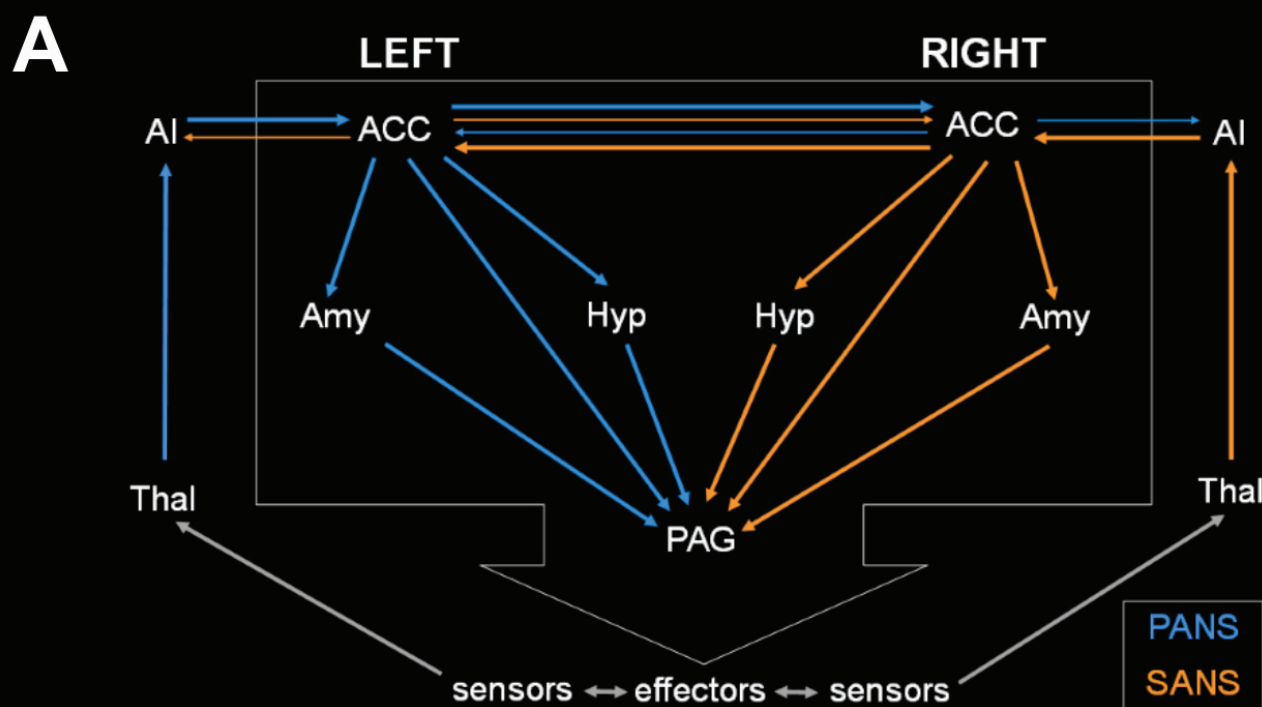
AUTONOMIC NETWORK ARCHITECTURE

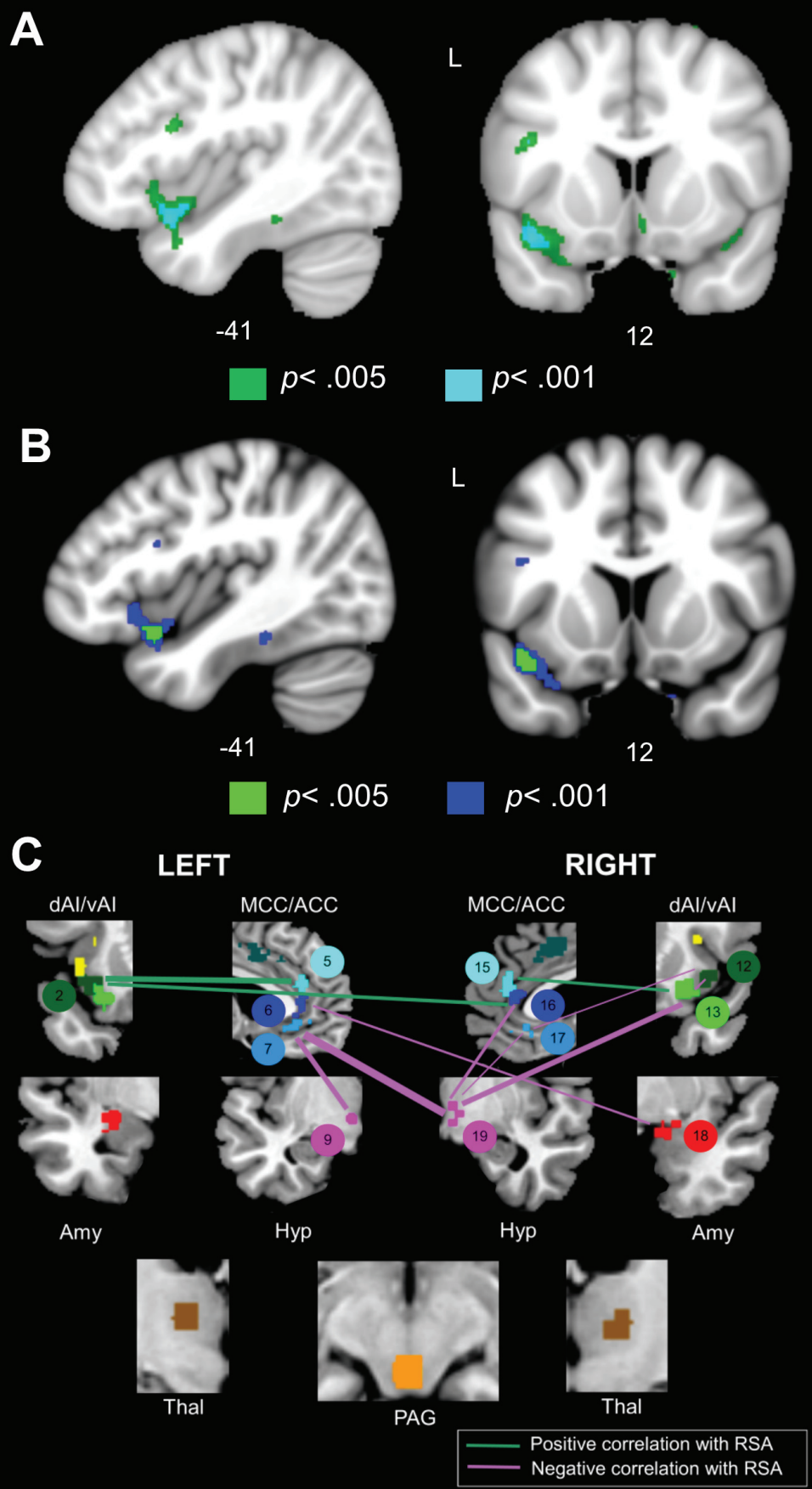
882 controlled for diagnosis in the regression models, these plots show that the association that we
883 detected between edge connectivity and resting autonomic activity were present in both
884 diagnostic groups and thus, were not driven by group membership. When we repeated the
885 original analyses in each diagnosis separately, RSA and SCL had similar associations with the
886 functional connectivity measures (Figure 4-1). See Figure 1 for abbreviations.

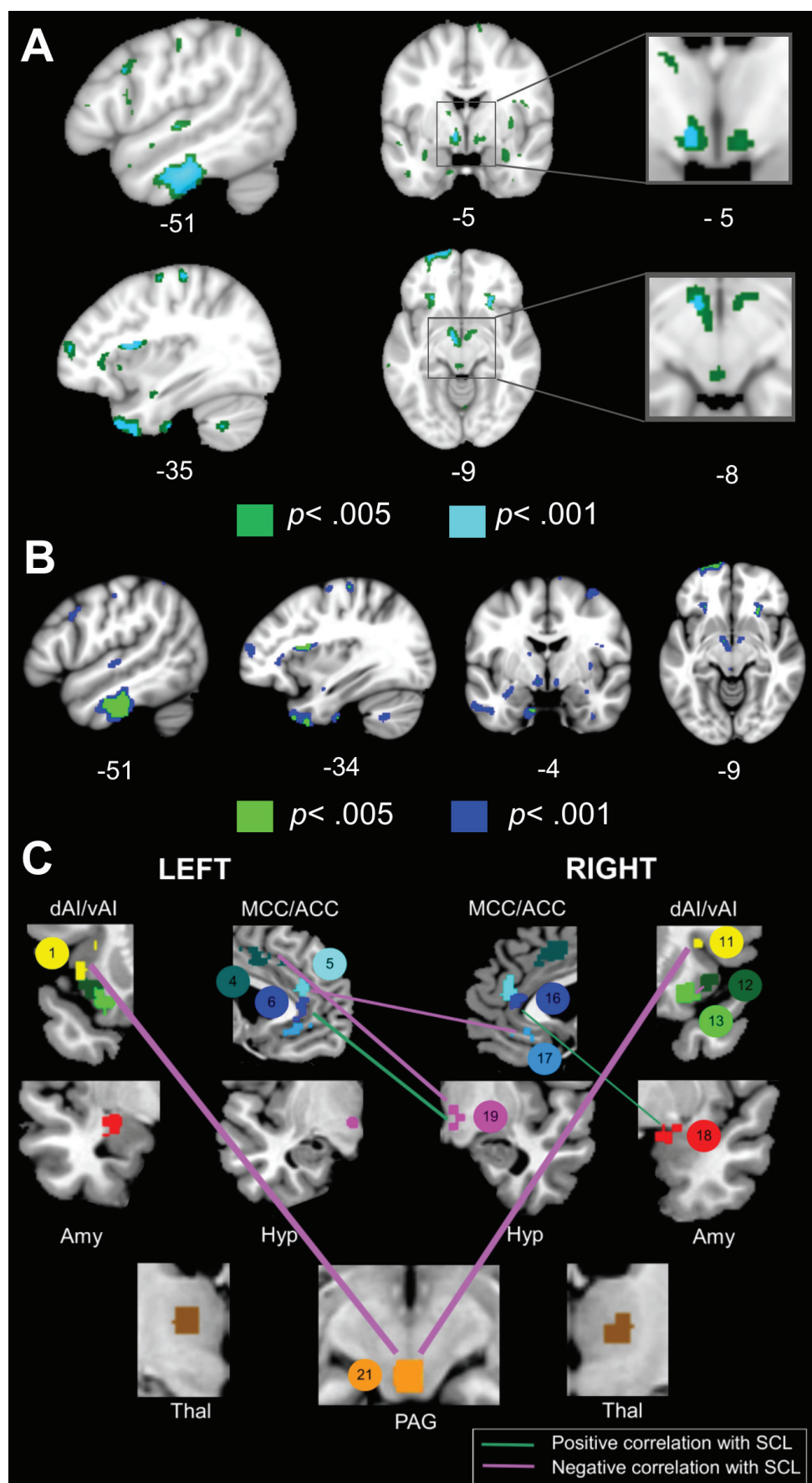
887 Figure 5

888 *Hypothesized RSA network.* Our results suggest that resting PANS tone depends on the integrity
889 of both strong and weak edges in the salience network. Stronger vAI – ACC connectivity and
890 weaker ACC – hypothalamus/amygdala connectivity was associated with higher resting RSA.
891 RSA, therefore, depends on intact connections between vAI (left > right) and ACC and weaker
892 connections between ACC and hypothalamus/amygdala (right > left), suggesting that nodes that
893 support SANS outflow must be inhibited to facilitate PANS activity. We hypothesize that PANS-
894 specific (e.g., ventrolateral PAG) and SANS-specific (e.g., dorsal PAG) subregions in each node
895 as well as untested connections with brainstem nuclei that are difficult to image (e.g., nucleus
896 ambiguus) may also play important roles in this network that we were not able to evaluate. Green
897 lines are edges in which stronger connectivity promoted RSA (i.e., edges 2–5, 2–16, and 13–15),
898 and purple lines are edges in which stronger connectivity inhibited RSA (i.e., 13–19, 7–9, 16–19,
899 17–19, and 6–18). * indicates edges that emerged as significant predictors of RSA in the
900 regression models. Laterality has been omitted for visual simplicity but is alluded to in the figure
901 layout. dPAG = dorsal PAG, vlPAG = ventrolateral PAG. See Figure 1 for other abbreviations.

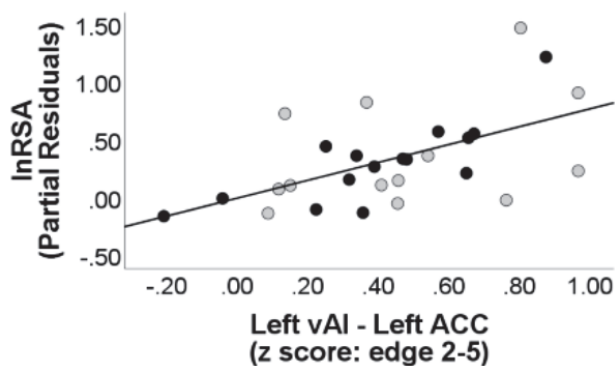
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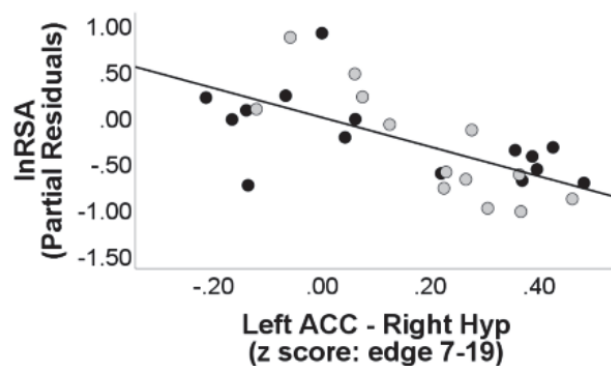




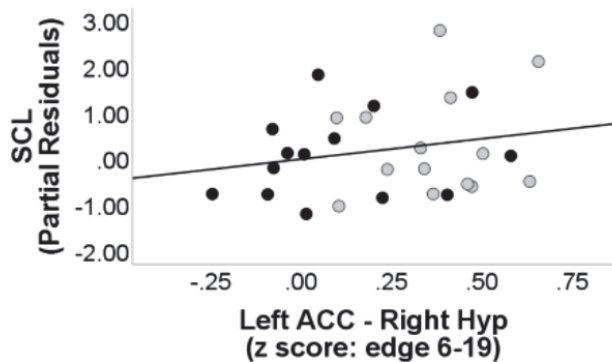
A Positive Correlation with RSA



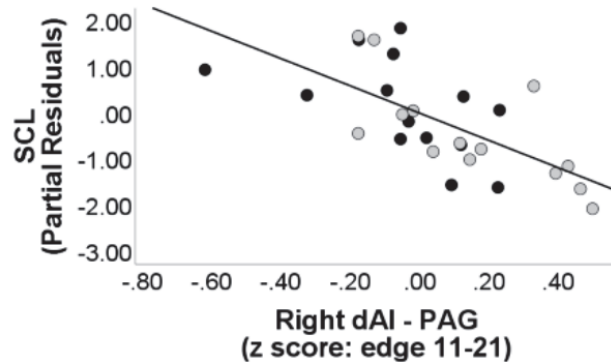
B Negative Correlation with RSA



C Positive Correlation with SCL



D Negative Correlation with SCL



Diagnosis ● bvFTD ● HC

